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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,609	06/26/2001	Leonidas Stamatatos	2570-1-001 N	8884

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/891,609	STAMATATOS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ ~~Notice of References Cited (PTO-892)~~

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03102004*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

Claims 24-28 stand withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 1-23 are currently under examination.

37 C.F.R. § 1.98

The information disclosure statement filed 10 March, 2004, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the

invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stamatatos and Cheng-Mayer (1998). As previously set forth, this teaching is directed toward SF162, a primary (PR), non-syncytium-inducing, macrophagetropic human immunodeficiency virus type 1 (HIV-1) clade B isolate which is resistant to antibody-mediated neutralization. It was reported that deletion of the first or second hypervariable envelope gp120 region (V1 or V2 loop, respectively) of this virus does not abrogate its ability to replicate in peripheral blood mononuclear cells and primary macrophages, nor does it alter its coreceptor usage profile. The mutant virus with the V1 loop deletion, SF162ΔV1, remains as resistant to antibody-mediated neutralization as the wild-type virus SF162. In contrast, **the mutant virus with the V2 loop deletion, SF162ΔV2, exhibits enhanced susceptibility to neutralization by certain monoclonal antibodies whose epitopes are located within the CD4-binding site and conserved regions of gp120.** More importantly, **SF162ΔV2 is now up to 170-fold more susceptible to neutralization than SF162 by sera collected from patients infected with clade B HIV-1 isolates.** In addition, **it becomes susceptible to neutralization by sera collected from patients infected with clade A, C, D, E, and F HIV-1 isolates. These**

findings suggest that the V2, but not the V1, loop of SF162 shields an as yet unidentified region of the HIV envelope rich in neutralization epitopes and that the overall structure of this region appears to be conserved among clade B, C, D, E, and F HIV-1 PR isolates. Thus, this teaching provides V2 region deleted HIV-1 viruses (SF162) comprising the same SEQ ID NOS.: set forth in claims 5 and 7. The recombinant envelope set forth in this publication can be neutralized by antisera from different viral clades. This teaching does not disclose methods of immunization against heterologous isolates employing the V2-deleted recombinants. However, the authors clearly and unambiguously state (see p. 7844, last paragraph) that **"The envelope of SF162ΔV2 could be used as an immunogen to generate antibodies against the exposed region. We believe that such antibodies would have a more potent cross-clade neutralizing potential than antibodies generated against the envelope of SF162."** Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to immunize a host against heterologous HIV-1 employing the SF162ΔV2 construct described by Stamatatos and Cheng-Mayer since they teach that such an immunogen would have potent cross-clade neutralizing activity and prove more valuable as an immunogen.

Applicants traverse and submit that the examiner must ascertain whether the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Applicants note that Stamatatos *et al.* (1998) fail to disclose the preparation of antibodies to the V2 deletion mutant or evidence that said antibodies display heterologous neutralizing activity. Applicants further argue that simply demonstrating that any given isolate can be neutralized *in vitro* by patient sera is not predictive of the ability of an immunogenic composition comprising the envelope of said isolate to induce a neutralizing antibody response *in vivo*. Applicants asserted that

four corroborative references were supplied with this response. **Applicants are advised that said references, as well as the accompanying supplemental information disclosure statement, were absent from the last response.**

Applicants' arguments have been carefully considered but are not deemed to be persuasive. The examiner does not concur with applicants' assessment that the skilled artisan would not reasonably expect the SF162ΔV2 construct to induce heterologous neutralizing antisera. The importance of this teaching is that it clearly illustrates that deletion of only the V2 region results in the presentation of broadly neutralizing epitopes that were not previously exposed. Applicants are again directed toward the last paragraph (p. 7844) of this article wherein the authors clearly state that "**Deletion of the V2 loop, but not the V1 loop, exposes highly conserved neutralization epitopes located within the core of the envelope protein and results in a dramatic increase in the susceptibility of the virus to neutralization by antibodies present in sera collected from patients infected with pan-clade HIV isolates. The envelope of SF162ΔV2 could be used as an immunogen to generate antibodies against the exposed region. We believe that such antibodies would have a more potent cross-clade neutralizing potential than antibodies generated against the envelope of SF162.**" The HIV-1 Env is highly immunogenic and the skilled artisan, absent evidence to the contrary, would reasonably expect this construct to induce broadly neutralizing antisera *in vivo*.

Applicants also provide four citations (Kim et al., 2003; Haigwood et al., 1990; Bolmstedt et al., 1996; Lu et al., 1998) in support of their arguments. Applicants are reminded that the claims are directed toward HIV-1 envelope proteins having a deletion in V2. The references supplied dealt with constructs having deletions in both V1 and V2 (V1/V2), V1-V3 (V1-V3), V3-V5, and V1-V5. However, none of these citations provided any data pertaining to HIV-1 envelopes carrying a single deletion in the V2 region. While these references suggest that deletion of the aforementioned

domains fails to generate broadly neutralizing antibodies, none of these publications dealt exclusively with V2 deletions. Moreover, the references relied upon in the rejection clearly demonstrate that V2 deletions are capable of inducing broadly neutralizing antisera as evidenced by the patient data. Applicants are reminded that the claims are simply directed toward an HIV-1 envelope comprising a V2 deletion that can induce immunity to at least one other HIV-1 strain. None of the claim limitations specify that the claimed invention is capable of inducing cross-clade neutralizing antibody response when used to immunize any given host.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

22 February, 2004